GB1529960

Title:
TREATING MAMMALS WITH 5-METHYL-1-PHENYL-2-(1H)PYRIDONE

Abstract:

1529960 Use of 5-methyl-1-phenyl-2 (1H)- pyridone AFFILIATED MEDICAL RESEARCH INC 9 Dec 1975 [9 Dec 1974] 50479/75 Heading A5B 5-Methyl-1-phenyl-2 (1H)-pyridone is administered to non-human mammals for reducing the serum glucose level, protecting the respiratory system, subject to noxious agents, alleviating or curing a deranged or infected respiratory system and alleviating at least one of the symptoms of dermatitis, insect sting and poison ivy. The active compound may be administered orally, topically, parenterally, intradermally or by inhalation in conventional forms and may be administered with other analgesics, sedatives, diuretics, stimulants, anti-arrhythmics and tranquillizers.

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PATENT SPECIFICATION (11) 1 529 960

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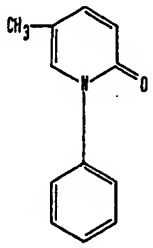
(19)

(54) TREATING MAMMALS WITH 5-METHYL-1-PHENYL-2-(1*H*)PYRIDONE

(71) We, AFFILIATED MEDICAL RESEARCH INC., of P.O. Box 5700, Princeton, New Jersey 08540, United States of America, a Body Corporate organized and existing under the laws of the State of New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to the treatment of certain ailments in non-human mammals using the compound 5 - methyl - 1 - phenyl - 2 - (1*H*) - pyridone, which is hereinafter referred to as AMR-69. AMR-69 has the formula:



In our co-pending Application No. 58642/73, Serial No. 1458048 we describe and claim pharmaceutical compositions containing AMR-69 and disclose that this compound has excellent analgesic activity, marked anti-inflammatory activity, shows excellent anti-pyretic activity (compared with a standard analgesic drug possessing these activities) and also causes significant lowering of uric acid levels in the serum after oral administration. We have now discovered that this compound, in addition to the valuable properties noted above also possesses the following valuable properties:

1. It causes significant lowering of glucose levels;
2. it is effective in the treatment of a number of ailments of the upper respiratory tract in humans and other mammals; and
3. it alleviates skin conditions, such as dermatitis and poison ivy.

Thus, the present invention consists in a method of reducing the serum glucose level of a non-human mammal having a high serum glucose level by administering 5 - methyl - 1 - phenyl - 2 - (1*H*) - pyridone to said mammal.

The invention further consists in a method of protecting the respiratory system of a non-human mammal subject to noxious agents against said agents by administering 5 - methyl - 1 - phenyl - 2 - (1*H*) - pyridone to said mammal.

A further aspect of the invention consists in a method of alleviating or curing a deranged or infected respiratory system of a non-human mammal by administering to said mammal 5 - methyl - 1 - phenyl - 2 - (1*H*) - pyridone.

The invention further consists in a method of alleviating at least one of the symptoms of dermatitis, insect sting and poison ivy on the skin of a non-human mammal by administering 5 - methyl - 1 - phenyl - 2 - (1*H*) - pyridone to said mammal.

AMR-69 has been observed to be therapeutically effective in protecting the mucous membranes of the respiratory system, particularly those of the nasopharynx and lungs, against noxious agents. Protection against noxious focal respiratory tract pathology (petechiae, oedema, haemorrhage and focal infection) has been demonstrated in gross examination of rat lung tissue and microscopic examination of dog lung tissue following treatment with AMR-69. The special protective effect on the mucous linings of the respiratory system has been confirmed in tests on humans, especially those showing symptoms of sinusitis, post-nasal drip, chronic rhinitis infection, allergic rhinitis, conjunctivitis, headache, earache and sore throat. We have also demonstrated the therapeutic effectiveness of AMR-69 against skin conditions, such as dermatitis, insect sting and poison ivy.

Administration of AMR-69 over extended

periods has been found to cause no untoward side effects. The compound is readily soluble in aqueous media, is very rapidly absorbed into the blood stream and is relatively non-irritating to the various body tissues at effective dosage levels. The preferred mode of administration depends upon the condition for which it is applied, but it may be administered orally, topically, parenterally, intradermally or by inhalation spray in formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term "parenteral" as used herein includes subcutaneous injection, intravenous injection, intramuscular injection, intracisternal injection, intrathecal injection or infusion techniques.

AMR-69 is preferably administered in unit dosage form, each unit dose preferably containing from 100 to 500 mg of the AMR-69.

AMR-69 may be administered in any conventional formulation appropriate to the mode of administration; thus, it may be formulated with: a solid carrier, diluent or coating; a liquid carrier, solvent or other diluent; or a gaseous carrier, to provide a pharmaceutical composition suitable for administration to mammals, especially to animals, such as horses, bovines, swine, dogs, cats, rats and mice, as well as to humans.

Solid carriers are useful for sub-dividing the active ingredient into pills, tablets, powders or cachets for immediate or sustained release or, where desirable, into suppositories or bougies. Solid diluents may include flavours or therapeutic adjuvants. Liquid carriers may be flavoured vehicles for oral administration. Alternatively, in the proper liquid form adjusted as to tonicity, the active ingredient may be formulated into solution or in liquid suspension for injectable administration, e.g. in water for injections; where a liquid carrier or diluent is employed to provide an injectable vehicle, it is normally sterile and pyrogen-free. Gaseous carriers or diluents are useful when formulating the active ingredient for aerosol administration, if indicated. Thus, the active ingredient, together with its solid carrier or diluent, can be pressed into unit dosage forms, such as pills or tablets, or encapsulated for sustained release; or it can be buffered, so as to dissolve in isotonic solutions for administration by injection. It can also be dispersed in suitable semi-solid carriers or liquids for topical administration, for local or systemic effect. Topical administration is particularly preferred where the AMR-69 is employed for the treatment of skin conditions.

As disclosed in our co-pending Application No. 58642/73, Serial No. 1458048, AMR-69 also has analgesic and uricosuric effects. It may be employed by itself in therapy or may be combined with other therapeutic agents; typical therapeutic agents with which it may be combined are other analgesics, sedatives, diuretics, stimulants, anti-arrhythmics and tranquilizers. The only known pharmacological incompatibility is with CNS stimulants, which may amplify pain beyond the analgesic capabilities of AMR-69. As the effects of AMR-69 appear to be exercised through a different enzyme system from that used by aspirin, it may advantageously be combined with aspirin in therapeutic compositions to achieve the combined effects of these agents, neither of which generates phenylhydrazine derivatives during catabolism.

AMR-69 may be prepared, as described in our co-pending Application No. 41074/75, Serial No. 1450049, by reacting 5 - methyl - 2 - (1*H*) - pyridone or a tautomer thereof with a halobenzene, preferably in the presence of an alkali metal carbonate and of finely divided metallic copper.

The invention is further illustrated with reference to the following Examples, of which Examples 1 and 2 describe formulations and Examples 3 and 4, which do not illustrate the invention claimed, show the effects of AMR-69 on humans.

EXAMPLE 1

Tablets containing AMR-69 as active ingredient

The following components were mixed together in amounts falling within the ranges given. We prefer that each tablet should contain from 100 to 500 mg of the active ingredient AMR-69.

AMR-69	100—500 mg.
Polyvinylpyrrolidone	2—4 mg.
Silicic acid	1 mg.
Corn Starch	40—80 mg.
Magnesium stearate	1—5 mg.
Talc	5—20 mg.
Milk Sugar	q.s.

Each of the mixtures was then granulated with commonly used moistening agents, such as glucose, syrups or water, and then compressed in a tablet-making machine. It will be understood that similar pharmaceutical formulations can also be prepared in the form of pills, dragees, capsules, cachets, suppositories, sustained release pulvules and similar pharmaceutical forms.

The posology of the compound in dosage form should, of course, be determined by the veterinary or physician. The individual dose should be adapted and adjusted to the patient's reactivity, the severity of the symptoms, the age, weight physical condition of the patient. For human subjects, a recommended dosage is from 200 mg to 400 mg per day for an average subject having a weight of about 75 kilograms. A more preferred range is from 300 to 400 mg. Because

of the low toxicity of AMR-69, however, higher doses can be used if the need arises. If desired or necessary, the above dosage can be repeated within from 4 to 6 hours.

EXAMPLE 2

Injectable solution

100 mg of AMR-69, 2.5 mg of sodium chloride and conventional buffers were dissolved in distilled water sufficient to provide 10 mg of AMR-69 per millilitre. This formulation was packaged in multiple dose vials and in individual ampoules.

In a similar manner, suspensions and solutions in liquid media, such as oils, syrups, tinctures and solvent solutions may be prepared. Petrolatum may be used as a vehicle for topical application.

EXAMPLE 3

Protection of mucous membranes of the nasopharynx and lungs against noxious agents

The effectiveness of treatment with AMR-69 in affording protection against focal respiratory tract pathology (petechiae, oedema, haemorrhage and focal infection) was demonstrated upon gross examination of rat lung tissue and microscopic examination of dog lung tissue following treatment of the animals with AMR-69. The special protective effects on the mucous linings of the respiratory system were also confirmed in clinical trials on humans exhibiting at least one of the following symptoms: sinusitis, post-nasal drip, chronic rhinitis infection, allergic rhinitis, conjunctivitis, headache, earache and sore throat. The pharmaceutical composition was administered orally in the form of capsules containing approximately 400 mg of AMR-69 per capsule. In these trials, the noxious effect of acute and chronic infections of the nasopharynx and cranial sinuses were arrested and relieved, as shown by cessation of congestion of the sinuses, disappearance of erythema of the mucous membranes, drainage of the sinuses and elimination of post-nasal drip. Evidence of relief from the symptom was observed within from 30 to 60 minutes after ingestion of the capsule.

EXAMPLE 4

Effect on skin conditions

The effectiveness of AMR-69 on skin conditions, such as dermatitis or itching, insect (bee) sting and poison ivy was demonstrated on humans exhibiting these symptoms following the procedure described in Example 3. Relief from the symptom was rapid in each case. It was observed in the case of a contact dermatitis condition (such as poison ivy) that application of AMR-69 in powder form directly on the affected skin areas provided substantially immediate relief from the characteristic itching and that weeping of the affected areas ceased within 30 minutes.

EXAMPLE 5

Reduction in serum glucose level

The effect of AMR-69 on glucose level in the serum (blood sugar level) was demonstrated on groups of 10 male and 10 female weanling rats of the Carworth Frams CFE strain. In a 9 week test, a group of male rats fed AMR-69 in the diet in an amount of 600 mg per kilogram body weight per day showed a mean value of 131.8 mg % of glucose in the serum; a group receiving 900 mg of AMR-69 per kilogram body weight per day showed a mean glucose value of 132.6 mg %; and a control male group receiving no AMR-69 showed a mean glucose value of 155.8 mg %.

A female group fed AMR-69 in the diet in an amount of 600 mg per kilogram body weight per day showed a mean glucose value of 144.8 mg %; a female group fed 900 mg per kilogram body weight per day showed a mean glucose value of 135.8 mg %; and a control group receiving no AMR-69 in the diet showed a mean glucose value of 173.0 mg %.

Details of acute toxicity in mice, primary eye irritation in rabbits and local toxicity in rabbit leg muscle of AMR-69 are given in our co-pending Application No. 58642/73, Serial No. 1458048.

We have found that AMR-69 differs markedly in its activity from closely related homologues, such as 5 - ethyl - 1 - phenyl - 2 - (1*H*) - pyridone (AMR-94), 3 - methyl - 1 - phenyl - 2 - (1*H*) - pyridone (AMR-77) and 1 - phenyl - 2 - (1*H*) - pyridone (AMR-93) in respect of therapeutic performance as well as toxicity characteristics. Thus, although AMR-69 was found to protect mucous membranes of the nasopharynx and lungs against noxious agents, AMR-93 and AMR-94 showed no protective effect and undesirable side effects were evident. AMR-77 showed no evidence of protective action. In general, use of AMR-93 and AMR-94 in several tests encompassing various types of pharmacological activity was accompanied by deleterious side effects; these side effects were not observed with AMR-77, but neither was any significant therapeutic activity.

WHAT WE CLAIM IS:—

1. A method of reducing the serum glucose level of a non-human mammal having a high serum glucose level by administering 5 - methyl - 1 - phenyl - 2 - (1*H*) - pyridone to said mammal.

2. A method of protecting the respiratory system of a non-human mammal subject to noxious agents against said agents by administering 5 - methyl - 1 - phenyl - 2 - (1*H*) - pyridone to said mammal.

3. A method of alleviating or curing a deranged or infected respiratory system of a

non-human mammal by administering to said mammal 5 - methyl - 1 - phenyl - 2 - (1*H*) - pyridone.

4. A method of alleviating at least one of the symptoms of dermatitis, insect sting and poison ivy on the skin of a non-human mammal by administering 5 - methyl - 1 - phenyl - 2 - (1*H*) - pyridone to said mammal.

5. A method according to any one of the preceding Claims, in which said 5 - methyl - 1 - phenyl - 2 - (1*H*) - pyridone is administered in admixture with a pharmaceutically acceptable adjuvant, carrier, diluent or coating.

6. A method according to any one of the preceding Claims, in which said 5 - methyl - 1 - phenyl - 2 - (1*H*) - pyridone is administered in unit dosage form.

7. A method according to Claim 6, in which each unit dose contains from 100 to 500 mg of 5 - methyl - 1 - phenyl - 2 - (1*H*) - pyridone.

8. A method according to Claim 2 or Claim 3, in which said mammal exhibits at least one of the symptoms of sinusitis, post-nasal drip, chronic rhinitis infection, allergic rhinitis, conjunctivitis, headache, earache and sore throat.

9. A method according to Claim 4, in which said 5 - methyl - 1 - phenyl - 2 - (1*H*) - pyridone is administered topically.

10. A method according to any one of Claims 1 to 8, in which said 5 - methyl - 1 - phenyl - 2 - (1*H*) - pyridone is administered in the form of tablets.

11. A method according to any one of Claims 1 to 8, in which said 5 - methyl - 1 - phenyl - 2 - (1*H*) - pyridone is administered by injection.

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